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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/001,278	11/01/2001	Robert V. Farese JR.	407T-927110US	2111

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/001,278	FARESE ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 27-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 27-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *04/14/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment filed on 10/14/2003 has been entered. Claims 12-26 and 38-56 have been canceled. Claims 1 and 27 have been amended. Claims 1-11 and 27-37 are pending and under consideration in the instant action.

Election/Restrictions

Applicant's election with traverse of Group I, clsim 1-11 and 27-37 in Paper No. 8 is acknowledged.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The rejection of claims 1-11 under 35 U.S.C. 101 is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 27-37 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In light of Applicants' amendments, the rejection based on the specification failing to describe more than one Ttpa gene is withdrawn.

The rejection based on the failure of the specification to describe transgenic knockout mammals produced through gene-targeted insertion in somatic cells is maintained (see page 3, last 2 lines-page 5, line 4 of the previous office action). Applicant argues that the Examiner alleges that knockout animals produced using nuclear transfer methods would produce knockout animals equivalent to those produced using ES cells. On the contrary, as stated in the previous office action, it cannot be predicted that animals generated using ES cell technology will have the same phenotype as genotypically identical animals created by somatic cell nuclear transfer. The state of the art at the time of filing was that the phenotype of animals generated through somatic cell nuclear transfer was highly unpredictable (refer to Dinnyes, 2002, Cloning and Stem Cells, Vol. 4, page 87, col. 1, 3rd full para.; McCreath, 2000, Nature, Vol. 405, paragraph bridging pages 1067-8) and that phenotypes effected by the procedure of nuclear transfer would arise independent of the gene disruption. The art also held that the phenotype of knockout mammals generated through ES cell technology was unpredictable. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and Technique,

Vol. 41, pages 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph). The specification describes a transgenic mouse generated using mouse ES cell comprising an insertional disruption in the Ttpa gene and, other than said mouse, does not describe any non-human mammal broadly encompassed by the claims. The specification teaches that a Ttpa mutation in humans causes a different phenotype than in the described mouse (paragraph 0144). Furthermore, the evidence of record provides no correlation between the knockout mouse generated by ES cell technology as described and any other species of Ttpa knockout. The art at the time of filing held that totipotent ES cell were not available for any species other than mouse (Campbell and Wilmut, 1997, Theriogenology, Vol. 47, pages 63-72). Therefore, the specification fails to adequately describe the broad genera of mammals encompassed by the claims.

Claims 1-11 and 27-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for i) a transgenic knockout mouse comprising a homozygous disruption in the endogenous *Ttpa* gene wherein the disruption is an insertion, deletion, frameshift, or stop codon and wherein the mouse exhibits a vitamin E deficiency or female infertility and ii) a transgenic knockout mouse comprising a heterozygous disruption in the endogenous *Ttpa* gene wherein the disruption is an insertion, deletion, frameshift, or stop codon and wherein the mouse exhibits vitamin E deficiency, does not reasonably provide enablement for any species of mammal comprising a disruption in any *Ttpa* gene wherein the animal has any phenotype other than vitamin E deficiency or female infertility. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The breadth of the claims encompasses any non-human species of animal comprising a disruption in the Ttpa gene wherein the mammal is generated through any means and wherein the disruption is an insertion, deletion, frameshift, stop codon or substitution and wherein the mammal exhibits a decreased level of α-TTP.

1) The rejection of the claims because the specification fails to enable making a knockout mammal other than mouse wherein said mammal exhibits any phenotype is maintained. The claims encompass generating knockout mammals using either targeted gene insertion in totipotent ES cells or either targeted gene insertion in somatic cells followed by nuclear transfer to generate a knockout mammal or through any other means, including RNAi. The claims encompass said mammal exhibiting any phenotype as a result of decreased α-TTP levels.

(a) With respect to the rejection on the grounds that the specification does not enable knocking out the Ttpa gene in any non-mouse species of mammal, Applicant argues that the nature of the invention is straightforward and that because the specification provides teachings relating to generating a viable knockout mouse using ES cell technology, one of skill in the art can produce a knockout mutant using any of a variety of techniques (page 9, 1st paragraph). It is maintained that the specification lacks the guidance necessary to generate a knockout animal using any technology other than ES cell technology. The specification has not even contemplated using other techniques, such as RNAi (see specification paragraph 0027; applicant's response, page 9, paragraph 1, line 4). With specific respect to generating mammals using somatic cell

nuclear transfer, the rejection is maintained for reason set forth in the previous office action (paragraph bridging pages 6-7).

Applicant argues that the examiner states that "there are no examples or guidance in the specification on how to reliably produce transgenic nematodes..." (page 10, paragraph 3). No reference has been found in the previous office action to transgenic nematodes and the basis of this argument and its relevance to the instant application is unclear. Applicant further argues that the methods used are applicable to other species of mammals (page 10, lines 7-9). On the contrary, it is maintained that the described ES cell technology used to generate knockout mice cannot be applied to other species of mammals as totipotent ES cells for non-mouse species are not available (refer to previous office action page 6, paragraph 2; Campbell and Wilmut, 1997). It would require undue experimentation for one of skill in the art to determine how to make the claimed species of mammals using cells other than totipotent ES cells or to generate totipotent ES cells from any non-mouse species.

Applicant argues that the level of skill in the art is high (typically with a Ph.D.) and that the production of knockout mutants is a routine technical exercise for one of such. This argument is not persuasive as one of skill in the art does not have the ability to generate totipotent ES cells from any non-mouse species (refer to Campbell and Wilmut and see above), one of skill in the art does not know, without additional experimentation, how to knockout the Ttpa gene through any means other than using ES cell technology. Applicant argues that it would not require undue experimentation to determine how to knockout the Ttpa gene in other species or through non-ES cell technology and that the simple screening is not undue experimentation.

The art at the time of filing held that ES cell technology was not developed for any species other than mouse (refer to Campbell and Wilmut, 1997, Theriogenology, Vol. 47, pages 63-72). The art also held that somatic cell nuclear transfer technology was underdeveloped and highly unpredictable. Phenotypes often arise in mammals generated by nuclear transfer that are independent of genotype (i.e. induced gene disruption; refer to Dinnyes, 2002, Cloning and Stem Cells, Vol. 4, pages 81-90; McCreath, 2000, Nature, Vol. 405, pages 1066-1069; Denning, 2001, Nature Biotechnology, Vol. 19, pages 559-562; Kent-First, 2000, Nature Biotecnology, Vol. 18, pages 928-929). Therefore, it is maintained that knocking out the Ttpa gene in ES cells to generate any non-mouse species would require undue experimentation. Furthermore, it is maintained that it would require undue experimentation to overcome the unpredictability set forth by the art for generating a knockout mammal of any species using any technology other than ES cell technology.

(b) With respect to the rejection on the grounds that the claims fail to recite a phenotype and therefore, the claims encompass mammals exhibiting any phenotype, Applicant argues that claims 1 and 27 recite the phenotype "decreased levels of α-tocopherol transfer protein (α-TTP) as compared to a wild-type animal." This phenotype is not well defined as argued by applicant (page 8, paragraph 4) and the specification fails to enable using an animal that merely has "decreased levels of α-tocopherol transfer protein (α-TTP) as compared to a wild-type animal." The specification fails to provide a correlation between decreased levels of α-tocopherol transfer protein and any phenotype encompassed by the claims. A knockout animal, by definition, will have decreased levels of α-tocopherol transfer protein (α-TTP) as compared to a wild-type animal. This is a defined result of a knockout mutation and does not describe the effect of

decreased levels of α-tocopherol transfer protein on the mammal. Phenotype is defined by The On-line Medical Dictionary (http://cancerweb.ncl.ac.uk/cgi-bin/omd?phenotype; 09 Jan 1998) as "The total characteristics displayed by an organism under a particular set of environmental factors, regardless of the actual genotype of the organism. Results from interaction between the genotype and the environment." The specification teaches that the mouse having a disruption in the Ttpa gene exhibits vitamin E deficiency (homozygotes and heterozygotes) or female infertility (homozygotes) but does not teach any other phenotype as broadly encompassed by the claims. One of skill in the art would not know how to make the claimed mammal exhibiting any phenotype or to use a mammal merely having a decreased level of α-tocopherol transfer protein. Therefore, the claims fail to recite a phenotype adequate for the claimed mammals.

2) The rejection of claims 8,9,34 and 35 on the grounds that the specification does not enable making chimeric mammals wherein the mammal comprises a disruption in Ttpa gene in only a somatic cell or only a germ cell is maintained for reason of record set forth in the paragraph bridging pages 8 and 9 of the previous office action. Applicant's general arguments with respect to the Wands factors as they apply to this rejection are not persuasive. It is maintained that the phenotype of chimeric animals is highly unpredictable, and generating one chimeric mammal provides no correlation to the phenotype of another chimeric mammal considering the number and spatial location of genetically disrupted cells will differ for each animal. Thus, the specification fails to overcome the unpredictability of phenotype in chimeric mammals. With respect to working examples, the specification provides no guidance as to how to generate chimeric mammals and provides no correlation between transgenic mammals comprising a disruption in the Ttpa gene in all cells and the claimed chimeras. With respect to

the quantity of experimentation required, simple screening is not all that is necessary to make and use the claimed chimeras. One of skill in the art would not know how to generate a chimera with a disruption in the Ttpa gene in the correct number of cells in the correct locations within the chimera to arrive at the desired chimeric mammal with the desired phenotype.

3) The rejection of claims 1-11 and 27-37 on the grounds that the specification fails to enable disrupting any othologous Ttpa gene is maintained. Applicant argues that one of skill in the art can knockout the Ttpa gene in any of a number of mammals without undue experimentation. This argument is not persuasive. As set forth above, the state of the art is such that knockout mammals other than mouse cannot be made. ES cell technology is not available for any species other than mouse and somatic cell nuclear transfer is highly unpredictable (see page 7, 1st paragraph). The specification fails to correlate a knockout od Ttpa orthologue in a non-mouse species using somatic cell nuclear transfer or any other method, and the phenotype of the mouse described in the instant specification.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of applicant's amendment, the rejection of claims 1 and 27 is withdrawn.

In light of applicant's argument, the rejection of claims 8,9,34 and 35 is withdrawn.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The rejection of claims 1-5, 8-11, 27-31 and 34-37 is maintained for reasons of record (refer to page 10 of the previous office action). Applicant argues that the priority date of the cited reference is not more than one year prior to the filing date of the present application (see applicant's response, page 12, paragraphs 2 and 3) and that a Katz declaration will be filed upon showing of allowable subject matter. The rejection is maintained for reasons of record. No Katz declaration has been received.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8-11, 27-31 and 34-47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (Scientific American, 1994, Vol. 240, pp. 34-41) in view of Fechner (Dec. 1999, Gen Bank Accession Number AF218416). The rejection is maintained for reasons of record set forth in the previous office action (pages 11-12).

Applicant argues that there was no reasonable expectation off success that viable Ttpa knockouts could be produced prior to the instant invention. However, applicant discloses that human with Ttpa gene defects are viable and there is no evidence of record indicating that disruption of the Ttpa gene would not lead to a viable mammal. Furthermore, the requirement for "success" is not clear. One of skill in the art would be motivated to combine the teaching of Capecchi and Fechner to generate a knockout mouse as it was an art recognized goal to determine the function of a gene product. It was reasonable, at the time the invention was made,

to expect that one of skill in the art could disrupt the Ttpa gene in a mouse and that mere disruption of the gene would meet the requirement of success. Viability is not required to successfully knockout a gene and result in a deficiency of functional gene product.

Applicant also argues that it is improper to consider the method of making the animals (page 13, (B)). Applicant cites In re Bell 26 USPQ2d 1529 (Fed. Cir. 1994) and In re Deuel 34 USPQ2d 1210 (Fed. Cir. 1995). These cases with relevance to claims to oligonucleotides and general methods of DNA isolation are not relevant or analogous to the instant claims. Applicant argues that the cited references fail to provide specific information about the particular claimed knockout animals. The claims fail to recite a phenotype specific to the claimed mammals and it is maintained that the claims, as broadly written, are anticipated by Capecchi and Fechner. The method of Capecchi is routine in the art and decreased or lack of α-Ttp production would be an expected result of knocking out the Ttpa gene. As stated in the previous office action, absent any phenotypic requirements for the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention. Capecchi discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning gene and the manifestation of disease (page 41, column 2, 2nd full paragraph).

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on Mon-Fri 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Note: After January 13, 2004, the Examiner may be reached at (571) 272-0725, and should the Examiner be unavailable, inquiries may be directed to Deborah Reynolds, SPE of Art Unit 1632 at (571) 272-0734.

Valarie Bertoglio
Patent Examiner

PETER PARAS
PATENT EXAMINER